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L2: Entry 1 of 1 File: USPT Jun 4, 2002

DOCUMENT-IDENTIFIER: US 6399761 B1
TITLE: Nucleic acid encoding human potassium channel K+ nov1 protein

US Patent No. (1):
6399761

Brief Summary Text (6):
Four transmembrane domain, tandem pore domain K+ channels (4T/2P channels) represent a new family of potassium selective ion channels involved in the control of background membrane conductances. In mammals, five channels fitting the 4T/2P architecture have been described: TWIK, TREK, TASK-1, TASK-2 and TRAAK. The 4T/2P channels all have distinct characteristics, but are all thought to be involved in maintaining the steady-state K.sup.+ potentials across membranes and therefore the resting potential of the cell near the equilibrium potential for potassium (Duprat et al. (1997) EMBO J 16(17):5464-5471). These proteins are particularly intriguing targets for therapeutic regulation. Within this group, TWIK-1, TREK-1 and TASK-1 and TASK-2 are widely distributed in many different tissues, while TRAAK is present exclusively in brain, spinal cord and retina. The 4T/2P channels have different physiologic properties; TREK-1 channels, are outwardly rectifying (Fink et al. (1996) EMBO J 15(24):6854-62), while TWIK-1 channels, are inwardly rectifying (Lesage et al. (1996) EMBO J 15(5):1004-11. TASK channels are regulated by changes in PH while TRAAK channels are stimulated by arachidonic acid (Reyes et al. (1998) JBC 273(47):30863-30869).

Brief Summary Paragraph Table (1):
TABLE 1 Chromosome Name cDNA SEQ Protein SEQ Polymorphisms Position Channel Type K + Hnov1 SEQ ID NO:1 SEQ ID NO:2 Alternative poly(A) tail: 1236, 2q37 ATP-sensitive inward rectifying 2395 K + Hnov4 SEQ ID NO:3 SEQ ID NO:4 A312C unknown Voltage gated K+ channel T335C A377G T344C A401G CA410-411GG (Ala/Thr) K + Hnov6 SEQ ID NO:5 SEQ ID NO:6 2p23 Delayed rectifying K+ channel K + Hnov9 SEQ ID NO:7 SEQ ID NO:8 Alternative poly(A) tail: 2304 8q23 Voltage gated K+ channel K + Hnov12 SEQ ID NO:9 SEQ ID NO:10 C321T (Pro/Leu) Xp21 Voltage gated K+ channel A375G (Glu/Gly) C407T (Leu/Phe) K + Hnov15 SEQ ID NO:11 SEQ ID NO:12 Alternative poly(A) tail: 1427 13q14 modulatory subunit A689G (Gly/Arg) K + Hnov27 SEQ ID NO:13 SEQ ID NO:14 T365A (Ile/Asn) 18q12 modulatory subunit K + Hnov2 SEQ ID NO:15 SEQ ID NO:16 N/A N/A 4 transmembrane domain, 2 pore domain K+ channel K + Hnov 11 SEQ ID NO:17 SEQ ID NO:18 N/A N/A Human ortholog of murine gene, 6 transmembrane dominas, voltage gated, delayed rectifier K+ channel K + Hnov 14 SEQ ID NO:19 SEQ ID NO:20 C3168T 12q14 6 transmembrane domain, voltage gated K+ channel K + Hnov28 SEQ ID NO:21-24 SEQ ID NO:25 4 alternative 5' splices 3q29 Modulatory subunit K + Hnov42 SEQ ID NO:26 SEQ ID NO:27 G1162A; T1460A; T2496A 8q11 Homology to K+ channel protein of C. elegans K + Hnov44 SEQ ID NO:28-29 SEQ ID NO:30 N/A 22p13 beta-subunit. K + Hnov49 SEQ ID NO:80 SEQ ID NO:81 (ATCT).sub.n repeats in the 3' 1q41 4T/2P channel; linked to the UTR sequence, starting at disease loci for rippling muscle position 2186 disease 1 (RMD1), and type II pseudohypoaldosteronism K + Hnov59 SEQ ID NO:82 SEQ ID NO:83 N/A chr19 4T/2P channel

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TITLE: Nucleic acid encoding human potassium channel K+ nov1 protein

US Patent No. (1):
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Brief Summary Text (14):
Sequences of four transmembrane, two pore potassium channels have been previously described. Reyes et al. (1998) J Biol Chem 273(47):30863-30869 discloses a pH sensitive channel. As with the related TASK-1 and TRAAK channels, the outward rectification is lost at high external K+ concentration. The TRAAK channel is described by Fink et al. (1998) EMBO J 17(12):3297-308. A cardiac two-pore channel is described in Kim et al. (1998) Circ Res 82(4):513-8. An open rectifier potassium channel with two pore domains in tandem and having a postsynaptic density protein binding sequence at the C terminal was cloned by Leonoudakis et al. (1998) J Neurosci 18(3):868-77.

Brief Summary Text (15):
The electrophysiological properties of Task channels are of interest, (Duprat et al. (1997) EMBO J 16:5464-71). TASK currents are K+-selective, instantaneous and non-inactivating. They show an outward rectification when external [K+] is low, which is not observed for high [K+]out, suggesting a lack of intrinsic voltage sensitivity The absence of activation and inactivation kinetics as well as voltage independence are characteristic of conductances referred to as leak or background conductances. TASK is very sensitive to variations of extracellular pH in a narrow physiological range, a property probably essential for its physiological function, and suggests that small pH variations may serve a communication role in the nervous system.

Brief Summary Text (25):
In many cases the functional ion channel formed by K+Hnov polypeptides will be heteromultimers. Heteromultimers are known to form between different voltage gated, outward rectifying potassium channel a subunits, generally comprising four subunits,

and frequently associated with auxiliary, .beta. subunits. Typically such .alpha. subunits share a six-transmembrane domain structure (S1-S6), with one. highly positively charged domain (S4) and a pore region situated between S5 and S6. Examples of such subunits are K+Hnov4, K+Hnov9, and K+Hnov12. Channels are also formed by multimerization of subunits of the two transmembrane and one pore architecture. It is predicted that two subunits of K+Hnov49 or K+Hnov59 will be required to form a functional channel.

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